5-Hydroxy Fatty Acid Amides from δ-Lactones and Alkyl Glucamines

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ABSTRACT: δ-Lactones derived from unsaturated fatty acids are useful precursors to fatty amides due to their enhanced reactivity. Consequently, temperature-sensitive glucamines were easily converted to their 5-hydroxy fatty acid amides in high yield (52–97%) by reaction with C_{18} and C_{20} δ-lactones. High yields of amides (52–97%) were obtained with little or no solvent at 90°C in less than 24 h. C_{18} δ-lactones were more miscible in the glucamine than the C_{20} δ-lactones and thus increased reaction rates and yields of amides. In addition, amidation reactions run in the absence of catalyst gave good yields, whereas reactions in the presence of base catalysts completely inhibited the reaction. The 1-(*N*-alkyl-5-hydroxy fatty acid amido)-D-glucitols are expected to have useful properties as biodegradable components in detergents.

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Meadowfoam (*Limnanthes alba*) is a crop currently cultivated in the Willamette valley of Oregon. Meadowfoam contains up to 85% Δ-5 unsaturated fatty acids. The Δ-5 unsaturated fatty acids can be converted to δ-lactones by an acid-catalyzed procedure developed by Isbell and Plattner (1). More recently, Isbell and Cermak (2) have also shown that δ-lactones could be obtained from other unsaturated acids such as oleic acid. The δ-eicosanolactones from meadowfoam and δ-stearolacetones from oleic acid are both very reactive species toward amines, with reaction rates several thousand times faster than the corresponding γ-lactones (3).

Interest in surfactants that are biodegradable and manufactured from renewable raw materials has been increasing at a rapid pace in recent years. Sugar fatty acid esters, one such group of surfactants, are used as industrial detergents and food emulsifiers in numerous products and processes (4). A regioselective, solvent-free esterification of simple alkyl glycosides using lipase derived from *Candida antarctica* has been described by Björkling *et al*. (5) and Adelhorost *et al*. (6). A second class of sugar-based surfactants are alkyl polyglucosides (APG), which are manufactured from fatty alcohols and sugars using acid catalysis. APG are now manufactured on a multimillion-pound scale. Alkyl polyglucosides are claimed to be manufactured from renewable materials and to be exceptionally mild to the skin.

A third class of sugar-based surfactants developed from renewable resources is the *N*-alkyl fatty acid glucamides as first described by Piggott (7) and later by Schwartz (8). However, due to several manufacturing difficulties this class of compounds failed to enter the market until Connor *et al*. (9,10) described an improved process. Several application patents have now been issued (11,12) on polyhydroxy fatty acid amides that are currently being manufactured. In addition, during the completion of this manuscript, Vermeer and Harichian (13) reported the coupling of short-chain δ-lactones with *N*-alkyl glucamides.

We herein describe new low-solvent and solvent-free processes that utilize long-chain δ-lactones and *N*-alkyl glucamines to yield 1-(*N*-alkyl-5-hydroxy fatty acid amido)-D-glucitols in high yields (Scheme 1).

EXPERIMENTAL PROCEDURES

Materials. Meadowfoam fatty acids were obtained by hydrolysis and distillation of meadowfoam oil supplied by the Fanning Corp. (Chicago, IL). δ-Lactones were prepared by the method of Isbell *et al*. (1,2). Ethanol was obtained from Quantum Chemical Co. (Tuscola, IL). Methanol, 2-propanol (IPA), and hexane were obtained from Fisher Scientific Co. (Fairlawn, NJ). *t*-Butyl alcohol was obtained from the Sigma Chemical Co. (St. Louis, MO). Filter paper was obtained from Whatman (Maidstone, England). Platinum on carbon catalyst (type B21142-5, Lot# C-2754) was a kind gift from Johnson Matthey (West Deptford, NJ). Lipase derived from *Pseudomonas* sp. was a generous gift from Boehringer-Mannheim (Indianapolis, IN). *N*-Methyl-D-glucamine and 1-amino-1-deoxy-D-sorbitol were purchased from Aldrich Chemical Co. (Milwaukee, WI).

Instrumentation. Reductive aminations were done using a high-pressure reaction vessel (Pressure Products Industries, Warminster, PA). High-performance liquid chroma-

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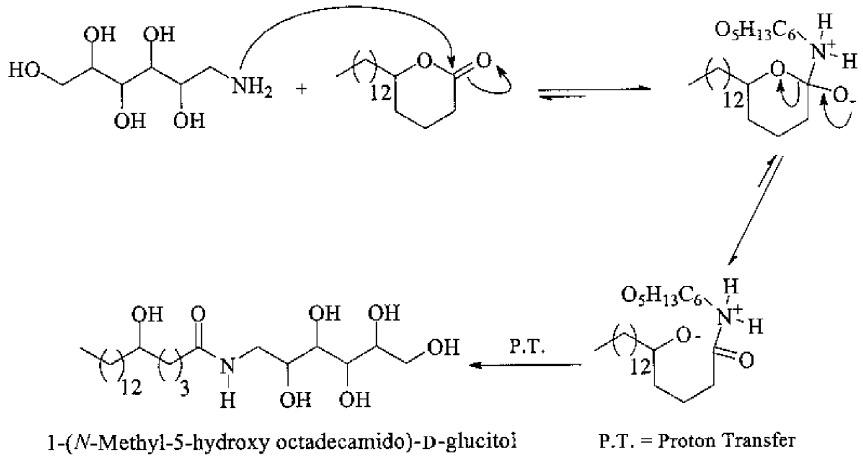

SCHEME 1

tography (HPLC) analysis of glucamine and glucamide mixtures was carried out using a Thermo Separations Products (Fremont, CA) spectra system AS1000 autosampler/injector with a P2000 binary gradient pump coupled to a Varex ELSD III light scattering detector (Alltech Associates Inc., Deerfield, IL). A Dynamax C-18 (Rainin Instrument Co., Woburn, MA) column (25 cm × 4.6 mm, 8 μm) was used to separate reaction mixtures by elution with an isocratic 95:5 methanol/water solvent mixture for reductive amination reactions and with 100% methanol for amidation reactions. A flow rate of 1 mL/min was used in all cases. The ELSD drift tube was set at 60°C, with the nebulizer set at 20 psi N_2 to provide a flow rate of 2.0 standard liters per minute (SLPM). Retention times for eluted peaks: *N*-methyl-D-glucamine, 2.7 min; 1-amino-1-deoxy-D-sorbitol, 2.8 min; *N*-propyl-D-glucamine, 2.9 min; *N*-(2-ethylhexyl)-D-glucamine, 3.0 min; 1-(5-hydroxy octadecamido)-D-glucitol, 3.9 min; 1-(*N*-methyl-5-hydroxy octadecamido)-D-glucitol, 3.9 min; 1-(*N*-propyl-5-hydroxy octadecamido)-D-glucitol, 4.0 min; 1-[*N*-(2-ethylhexyl)-5-hydroxy octadecamido]-D-glucitol, 4.4 min; 1-(5-hydroxy eicosamido-D-glucitol, 4.4 min; 1-(*N*-methyl-5-hydroxy eicosamido)-D-glucitol, 4.4 min; 1-(*N*-propyl-5-hydroxy eicosamido)-D-glucitol, 4.5 min; 1-[*N*-(2-ethylhexyl)-5-hydroxy eicosamido]-D-glucitol, 5.1 min; δ-stearolacetone, 5.2 min; δ-eicosanolactone, 6.3 min.

^1H and ^{13}C NMR spectra were obtained on a Bruker ARX-400 with a 5-mm dual proton/carbon probe, using CD_3OD as solvent. Elemental analysis was performed by Desert Analytics (Tucson, AZ). All samples were recrystallized and dried at 100°C under vacuum before analysis.

N-*Propyl-D-glucamine*. Glucose (10.0 g, 25.4 mmol) was dissolved in methanol (40 mL), followed by the addition of propylamine (1.50 g, 25.4 mmol) and 2% w/w of platinum on carbon (0.32 g dry weight). The mixture was transferred to a 100-mL pressure reactor, blanketed with 50 atm H_2, and then heated to 60°C with constant stirring for 1–12 h. After the reaction was complete, the mixture was vacuum-filtered and excess propylamine and methanol were removed by a rotary evaporator (rotovap) at room temperature. Product distribution was monitored by reversed-phase HPLC (conditions described above).

^1H NMR of *N*-propyl-glucamine: δ 3.89–3.56 (*m*, 6H, HOCH_2–C*H*OH–C*H*OH–C*H*OH–C*H*OH–), 2.79–2.65 (*m*, 2H, –N–CH_2–), 2.60–2.48 (*m*, 2H, –N–CH_2–), 1.31–1.28 (*m*, 2H, –CH_2–CH$_3$), and 0.94 ppm (*t*, *J* = 7.4 Hz, 3H, –CH_3). ^{13}C NMR of *N*-propyl-glucamine: δ 72.9 (*d*), 72.5 (*d*), 72.5 (*d*), 72.4 (*d*), 64.9 (*t*), 52.4 (*t*), 48.3 (*t*), 23.5 (*t*), and 12.0 ppm (*q*).

N-*(2-Ethylhexyl)-D-glucamine*. Glucose (10.0 g, 25.4 mmol) was dissolved in methanol (40 mL), followed by the addition of 2-ethylhexylamine (3.28 g, 25.4 mmol) and 2% w/w of platinum on carbon (0.26 g, dry weight). The mixture was transferred to a 100-mL pressure reactor, blanketed with 50 atm H_2, and then heated to 60°C for 1–12 h. After the reaction was complete, the mixture was vacuum filtered, and excess 2-ethylhexylamine and methanol were removed by rotovap at room temperature. Product distribution was monitored by reversed-phase HPLC (conditions described above).

^1H NMR of *N*-(2-ethylhexyl)-D-glucamine as a mixture of diastereomers: δ 3.87–3.58 (*m*, 6H, HOCH_2–C*H*OH, –C*H*OH–C*H*OH–C*H*OH–), 2.75–2.72 (*m*, 2H, N–CH_2–), 2.58–2.45 (*m*, 2H, N–CH_2–), 1.5–1.28 (m, 9H, –CH_2–C*H*–CH_2–CH_2–CH_2–), 0.91 (*t*, *J* = 6.7 Hz, 3H, –CH_3), and 0.89 ppm (*t*, *J* = 7.4 Hz, 3H, –CH_3). ^{13}C NMR of *N*-(2-ethylhexyl)-D-glucamine as a mixture of diastereomers: δ 72.8 (*d*), 72.7 (*d*), 72.5 (*d*), 72.4 (*d*), 65.0 (*t*), 53.9 (*t*), 52.5 (*t*), 40.3 (*d*), 32.3 (*t*), 30.0 (*t*), 25.4 (*t*), 24.1 (*t*), 14.4 (*q*), and 11.1 ppm (*q*).

1-(5-Hydroxy octadecamido)-D-glucitol (**I**). 1-Amino-1-deoxy-D-sorbitol (1.00 g, 5.52 mmol) and δ-stearolactone (1.56 g, 5.52 mmol) were dissolved in *t*-butyl alcohol (20 mL). The reaction was mixed with a magnetic stirrer and heated to 82°C for 21 h to yield a brown product. The yield was 92% of **I** as measured by HPLC. Amide **I** was then concentrated *in vacuo* to yield a white precipitate. The precipitate was dissolved in 1–5 vol of methanol, cooled from –25 to

–80°C until crystals formed, filtered and dried to remove excess amine. Recrystallization from 1–5 volumes of hexane at –25 to –80°C to remove excess lactone and fatty acid gave white crystals of **I** as a mixture of diastereomers.

^{1}H NMR of **I** as a mixture of diastereomers: δ 3.80–3.47 (*m*, 7H, –C*H*OH, –HOCH_2–C*H*OH–, –C*H*OH–C*H*OH–C*H*OH–), 3.43 (*dd*, *J* = 13.8, 4.8 Hz, 1H, diastereomer A, –NH–CH_aH$_b$–CHOH–), 3.23 (*dd*, *J* = 13.8, 7.3 Hz, 1H, diastereomer A, –NH–CH$_a$$H_b$–CHOH–), 2.93 (*dd*, *J* = 12.9, 4.0 Hz, 1H, diastereomer B, –NH–CH_aH$_b$–CHOH–), 2.84 (*dd*, *J* = 12.9, 7.3 Hz, 1H, diastereomer B, –NHCH$_a$$H_b$–CHOH–), 2.22–2.11 (*m*, 2H, –CH_2–CO–N), 1.78–1.25 (*m*, 28H, –CH_2–), and 0.89 ppm (*t*, *J* = 7.1 Hz, 3H, –CH_3). ^{13}C NMR of **I** as a mixture of diastereomers: δ 176.7 (*s*), 73.7 (*d*), 73.4 (*d*), 73.3 (*d*), 73.0 (*d*), 72.9 (*d*), 72.7 (*d*), 72.1 (*d*), 72.0 (*d*), 71.3 (*d*), 64.8 (*t*), 44.0 (*t*), 43.4 (*t*), 38.4 (*t*), 37.8 (*t*), 37.0 (*t*), 33.0 (*t*), 30.8 (*t*), 30.8 (*t*), 30.4 (*t*), 26.8 (*t*), 23.7 (*t*), 23.6 (*t*), 23.2 (*t*), and 14.4 ppm (*q*). Calculated elemental analysis of **I**: C, 62.17; H, 10.65; N, 3.02. Found: C, 62.02; H, 10.71; N, 3.17.

*1-(*N*-Methyl-5-hydroxy octadecamido)-*D*-glucitol* (**II**). δ-Stearolacetone (4.00 g, 14.19 mmol) and *N*-methyl-D-glucamine (2.78 g, 14.22 mmol) were mixed at 90°C, using a mechanical stirrer in a water-heated reactor. The reaction was stopped after 16 h to yield a white product. HPLC analysis indicated a 97% yield of glucitol **II** as a mixture of diastereomers. Glucitol **II** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **II** as a mixture of diastereomers: δ 3.99–3.92 (*m*, 1H, –CH_2–CHOH–), 3.79–3.74 (*m*, 2H, HOCH_2–CHOH–), 3.71–3.47 (*m*, 4H, –C*H*OH–C*H*OH–C*H*OH–, C*H*OH–; 1H, diastereomer A, –N–CH_aH$_b$–), 3.45–3.35 (*m*, 2H, diastereomer B, –NC$H_a$$H_b$–) 3.45–3.35 (*m*, 1H, diastereomer A, –N–CH$_a$$H_b$), 3.13 (*s*, 3H, diastereomer B, –N–CH_3), 2.96 (*s*, 3H, diastereomer A, –N–CH_3), 2.55–2.35 (*m*, 2H, –CH_2–CO–N–), 1.79–1.25 (*m*, 28H, –CH_2–), and 0.89 ppm (*t*, *J* = 7.1 Hz, 3H, –CH_3). ^{13}C NMR of **II** as a mixture of diastereomers: δ 176.6 (*s*), 176.5 (*s*), 74.3 (*d*), 73.5 (*d*), 73.2 (*d*), 73.1 (*d*), 73.0 (*d*), 72.8 (*d*), 72.1 (*d*), 71.6 (*d*), 71.1 (*d*), 64.7 (*d*), 53.8 (*t*), 52.5 (*t*), 38.5 (*t*), 38.5 (*t*), 38.0 (*q*), 37.9 (*t*), 34.6 (*q*), 34.6 (*t*), 34.4 (*t*), 34.0 (*t*), 33.1 (*t*), 30.9 (*t*), 30.8 (*t*), 30.5 (*t*), 26.8 (*t*), 23.7 (*t*), 22.8 (*t*), 22.8 (*t*), 22.4 (*t*), and 14.4 ppm (*q*). Calculated elemental analysis of **II**: C, 62.86; H, 10.76; N, 2.93. Found: C, 62.86; H, 10.78; N, 2.95.

*1-(*N*-Propyl-5-hydroxy octadecamido)-*D*-glucitol* (**III**). *N*-Propyl-D-glucamine (1.00 g, 4.48 mmol) and δ-stearolactone (1.26 g, 4.48 mmol) were mixed at 90°C, using a mechanical stirrer in a water-heated reactor. The reaction was stopped after 19 h to yield a white product. HPLC analysis indicated a 74% yield of **III** as a mixture of diastereomers. Glucitol **III** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **III** as a mixture of diastereomers: δ 3.99–3.92 (*m*, 1H, –CH$_2$–C*H*OH–), 3.78–3.20 (*m*, 10H, –C*H*OH–, HOCH_2–C*H*OH–C*H*OH–C*H*OH–, –N–CH_2–CH$_2$–, –N–CH_2–CHOH–), 2.51–2.35 (*m*, 2H, –CH_2–CO–N–), 1.78–1.23 (*m*, 30H, –CH_2–), and 0.95–0.86 ppm (*m*, 6H, –CH_3). ^{13}C NMR of **III** as a mixture of diastereomers: δ 176.5 (*s*) , 176.4 (*s*), 74.3 (*d*), 73.5 (*d*), 73.2 (*d*), 73.1 (*d*), 73.0 (*d*), 72.8 (*d*), 72.1 (*d*), 71.6 (*d*), 71.1 (*d*), 64.7 (*t*), 52.4 (*t*), 51.6 (*t*), 50.5 (*t*), 49.8 (*t*), 38.5 (*t*), 38.5 (*t*), 37.9 (*t*), 34.0 (*t*), 33.9 (*t*), 33.1 (*t*), 30.9 (*t*), 30.8 (*t*), 30.8 (*t*), 30.5 (*t*), 26.8 (*t*), 23.7 (*t*), 23.0 (*t*), 22.9 (*t*), 21.5 (*t*), 14.4 (*q*), 11.6 (*q*), and 11.4 ppm (*q*). Calculated elemental analysis of **III**: C, 64.12; H, 10.96; N, 2.77. Found: C, 64.50; H, 10.98; N, 2.56.

*1-(*N*-(2-Ethylhexyl)-5-hydroxy octadecamido)-*D*-glucitol* (**IV**). *N*-2-(Ethylhexyl)-D-glucamine (1.00 g, 3.41 mmol) and δ-stearolactone (0.96 g, 3.41 mmol) were mixed with *t*-butyl alcohol (20 mL), stirred with a magnetic stirrer, and heated to 82°C. The reaction was stopped after 64 h to yield 67% of **IV** as a mixture of diastereomers, a white product. **IV** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **VII** as a mixture of diastereomers: δ 4.05–3.93 (*m*, 1H, –CH$_2$–C*H*OH–), 3.85–3.10 (*m*, 10H, –C*H*OH–, HOCH_2–C*H*OH–C*H*OH–C*H*OH, –N–CH_2–, –N–CH_2–CHOH), 2.55–2.31 (*m*, 2H, –CH_2–CO–N–), 1.80–1.21 (*m*, 37H, –CH_2–, –C*H*–), and 0.95–0.86 ppm (*m*, 9H, –CH_3). ^{13}C NMR of **VII** as a mixture of diastereomers: δ 176.7 (*s*), 74.3 (*d*), 73.1 (*d*), 73.0 (*d*), 72.9 (*d*), 72.9 (*d*), 72.3 (*d*), 72.1 (*d*), 64.7 (*t*), 54.2 (*t*), 53.2 (*t*), 51.6 (*t*), 50.3 (*t*), 49.2 (*t*), 40.1 (*d*), 38.6 (*t*), 38.4 (*t*), 38.3 (*t*), 37.9 (*t*), 34.8 (*t*),34.5 (*t*), 33.1 (*t*), 31.7 (*t*), 30.8 (*t*), 30.8 (*t*), 30.5 (*t*), 26.5 (*t*), 24.9 (*t*), 24.8 (*t*), 24.2 (*t*), 24.1 (*t*), 23.7 (*t*), 23.0 (*t*), 22.9 (*t*), 21.5 (*t*), 14.4 (*q*), 16.6 (*q*), and 10.6 ppm (*q*). Calculated elemental analysis of **VII**: C, 66.74; H, 11.38; N, 2.43. Found: C, 66.50; H, 11.40; N, 2.60.

*1-(5-Hydroxy eicosamido)-*D*-glucitol* (**V**). 1-Amino-1-deoxy-D-sorbitol (5.85 g, 32.3 mmol) and δ-eicosanolactone (10.0 g, 32.3 mmol) were dissolved in ethanol (50 mL). The reaction was heated to reflux for 16 h and stirred magnetically to yield a light-colored product. HPLC analysis indicated a 82% yield of **V** as a mixture of diastereomers. Glucitol **V** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **V** as a mixture of diastereomers: δ 3.82–3.46 (*m*, 7H, –C*H*OH, –OCH_2– C*H*OH–, C*H*OH–C*H*OH–C*H*OH–), 3.45 (*dd*, *J* = 13.8, 4.8 Hz, 1H, diastereomer A, –NH– CH_aH$_b$ –CHOH–), 3.26 (*dd*, *J* = 13.8, 7.1 Hz, 1H, diastereomer A, –NH–CH$_a$$H_b$–CHOH–), 2.85 (*m*, 2H, diastereomer B, NH–C$H_a$$H_b$–CHOH–), 2.24–2.20 (*m*, 2H, –CH_2–CO–N–), 1.70–1.60 (*m*, 2H, –CH_2–CH$_2$–CO–N–), 1.46–1.21 (*m*, 30H, –CH_2–), and 0.88 ppm (*t*, *J* = 7.1 Hz, 3H, –CH_3). ^{13}C NMR of **V** as a mixture of diastereomers: δ 176.7 (*s*), 74.0 (*d*), 73.8 (*d*), 73.3 (*d*), 73.3 (*d*), 73.3 (*d*), 73.2 (*d*), 72.3 (*d*), 72.2 (*d*), 71.6 (*d*), 64.9 (*t*), 44.5 (*t*), 43.6 (*t*), 38.4 (*t*), 37.8 (*t*), 37.1 (*t*), 32.9 (*t*), 30.8 (*t*), 30.6 (*t*), 30.3 (*t*), 26.7 (*t*), 23.6 (*t*), 23.1 (*t*), and 14.2 ppm (*q*). Calculated elemental analysis of **V**: C, 63.51; H, 10.86; N, 2.85. Found: C, 63.77; H, 10.88; N, 2.72.

*1-(*N*-Methyl-5-hydroxy eicosamido)-*D*-glucitol* (**VI**). *N*-Methyl-D-glucamine (1.00 g, 5.12 mmol) and δ-eicosanolactone (1.58 g, 5.12 mmol) were dissolved in *t*-butyl alcohol (20 mL) . The reaction was heated to 82°C for 64 h and magnetically stirred to give a white product. HPLC analy-

sis indicated a 79% yield of glucitol **VI** as a mixture of diastereomers. Glucitol **VI** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **VI** as a mixture of diastereomers: δ 4.00–3.92 (m, 1H, –CH_2–C*H*OH–), 3.81–3.73 (*m*, 2H, HOCH_2–CHOH–), 3.72–3.49 (*m*, 4H, –C*H*OH–C*H*OH–C*H*OH–C*H*OH–, 1H, diastereomer A, –NC$H_a$$H_b$–), 3.48–3.35 (*m*, 2H, diastereomer B, –N–C$H_a$$H_b$–), 3.48–3.35 (*m*, 1H, diastereomer A, N–C$H_a$$H_b$–), 3.13 (*s*, 3H, diastereomer B, –N–CH_3), 2.96 (*s*, 3H, diastereomer A, –N–CH_3), 2.54–2.33 (*m*, 2H, –CH_2–CH_2–CON–), 1.79–1.25 (*m*, 32H, – CH_2–), and 0.89 ppm (*t*, *J* = 7.1 Hz, 3H, –CH_3). ^{13}C NMR of **VI** as a mixture of diastereomers: δ 176.5 (*s*), 176.5 (*s*), 74.1 (*d*), 73.0 (*d*), 72.9 (*d*), 72.8 (*d*), 72.2 (*d*), 72.2 (*d*), 72.1 (*d*), 71.5 (*d*), 71.1 (*d*), 64.7 (*t*), 53.9 (*t*), 52.5 (*t*), 38.5 (*t*), 38.0 (*q*), 37.9 (*t*), 34.6 (*q*), 34.6 (*t*), 34.4 (*t*), 34.0 (*t*), 33.1 (*t*), 30.9 (*t*), 30.8 (*t*), 30.5 (*t*), 26.8 (*t*), 23.7 (*t*), 22.8 (*t*) 22.7 (*t*), 22.4 (*t*), and 14.5 ppm (*q*). Calculated elemental analysis of **VI**: C, 64.12; H, 10.96; N, 2.77. Found: C, 64.52; H, 11.17; N, 2.75.

1-(N-Propyl-5-hydroxy eicosamido)-D-glucitol (**VII**). δ-Eicosanolactone (1.00 g, 3.23 mmol) and *N*-propyl-D-glucamine (0.707 g, 3.23 mmol) were mixed at 90°C, using a mechanical stirrer in a water-heated reactor. The reaction was stopped after 18 h to yield a brown-colored product. HPLC analysis showed a 76% yield of glucitol **VII** as a mixture of diastereomers. Glucitol **VII** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **VII** as a mixture of diastereomers: δ 4.05–3.93 (*m*, 1H, –CH_2–C*H*OH–), 3.81–3.20 (*m*, 10H, –C*H*OH–, HOCH_2–C*H*OH–C*H*OH–C*H*OH–, N-CH_2–CHOH, N–CH_2–CH_2–), 2.51–2.30 (*m*, 2H, –CH_2–CO–N–), 1.78–1.25 (*m*, 34H, –CH_2–), and 0.92–0.85 ppm (*m*, 6H, –CH_3). ^{13}C NMR of **VII** as a mixture of diastereomers: δ 176.5 (*s*), 176.4 (*s*), 74.3 (*d*), 73.6 (*d*), 73.2 (*d*), 73.1 (*d*), 73.0 (*d*), 72.8 (*d*), 72.1 (*d*), 71.6 (*d*), 71.1 (*d*), 64.7 (*t*), 52.4 (*t*), 51.6 (*t*), 51.0 (*t*), 50.5 (*t*), 38.5 (*t*), 38.5 (*t*), 37.9 (*t*), 33.9 (*t*), 33.1 (*t*), 30.9 (*t*), 30.8 (*t*), 30.5 (*t*), 26.8 (*t*), 23.7 (*t*), 23.0 (*t*), 22.9 (*t*), 21.5 (*t*), 14.4 (*q*), 11.6 (*q*), and 11.4 ppm (*q*). Calculated elemental analysis of **VII**: C, 65.25; H, 11.14; N, 2.62. Found: C, 65.23; H, 11.24; N, 2.39.

1-(N-(2-Ethylhexyl)-5-hydroxy eicosamido)-D-glucitol (**VIII**). δ-Eicosanolactone (3.01 g, 9.71 mmol) and *N*-(2-ethylhexyl)-D-glucamine (2.85 g, 9.73 mmol) were dissolved in *t*-butyl alcohol (50 mL) in a 100-mL round-bottom flask. The magnetically stirred reaction was heated to 82°C for 130 h to yield 52% of **VIII** as a mixture of diastereomers. Glucitol **VIII** was recovered from the reaction mixture by the same procedure as **I**.

^{1}H NMR of **VIII** as a mixture of diastereomers: δ 4.04–3.96 (*m*, 1H, –CH_2–C*H*OH–), 3.86–3.10 (*m*, 10H, –C*H*OH, HOCH_2–C*H*OH–C*H*OH–C*H*OH, –N–CH_2–, –N–CH_2–CHOH), 2.55–2.28 (*m*, 2H, –CH_2–CO–N–), 1.79–1.21 (*m*, 41H, –CH_2–, –C*H*–), and 0.98–0.84 ppm (*m*, 9H, –CH_3). ^{13}C MNR of **VIII** as a mixture of diastereomers: δ 176.7 (*s*), 74.3 (*d*), 73.2 (*d*), 73.0 (*d*), 72.9 (*d*), 72.9 (*d*), 72.3 (*d*), 72.1 (*d*), 64.7 (*t*), 54.3 (*t*), 53.2 (*t*), 50.3 (*t*), 49.2 (*t*), 40.1 (*d*), 38.6 (*t*), 38.4 (*t*), 38.3 (*t*), 37.9 (*t*), 34.8 (*t*), 34.5 (*t*), 33.1 (*t*), 31.7 (*t*), 30.8 (*t*), 30.8 (*t*), 30.8 (*t*), 30.5 (*t*), 26.8 (*t*), 24.9 (*t*), 24.8 (*t*), 24.2 (*t*), 24.1 (*t*), 23.7 (*t*), 23.0 (*t*), 22.9 (*t*), 21.5 (*t*), 14.3 (*q*), 11.5 (*q*), and 10.6 ppm (*q*). Calculated elemental analysis of **VIII**: C, 67.62; H, 11.52; N, 2.32. Found: C, 67.83; H, 11.64; N, 2.42.

RESULTS AND DISCUSSION

1-(*N*-Alkyl-5-hydroxy fatty acid amido)-D-glucitols were synthesized in high yield in the absence of catalyst as shown in Scheme 1. Table 1 outlines the scope of the chemistry for the synthesis of amides from δ-lactones and alkyl glucamine. Reactions were successful in the absence of solvent with near quantitative yields when appropriate alkyl groups were selected for the alkyl glucamine. Methyl glucamine yielded 97% yield of amide due to its good miscibility with δ-stearolactone. In the absence of solvent, however, unsubstituted glucamine displayed little to no reactivity with δ-lactones due to the insolubility of the δ-lactones in glucamine. However, reactions run in *t*-butyl alcohol yielded 92% amide with δ-stearolactone. Glucamine and δ-eicosanolactone gave 82% of amide when ethanol was used as solvent. As the length of the alkyl substituent on the glucamine increased, yields of amides decreased, possibly due to steric interactions of the amine nucleophile with the δ-lactone, although solubility of the glucamine increased.

TABLE 1
Synthesis of 5-Hydroxy Alkyl-*N*-glucamides[a]

Lactone	Glucamine[a] R =	Reaction time (h)	Solvent	Temperature (°C)	Yield of 5-hydroxy alkyl-*N*-glucamides[b] (%)
δ-C_{18}	H	21	*t*-BuOH	82	92
δ-C_{18}	Methyl	16	No solvent	90	97
δ-C_{18}	Propyl	19	No solvent	90	74
δ-C_{18}	2-Ethylhexyl	64	*t*-BuOH	82	67[c]
δ-C_{20}	H	16	Ethanol	82	82
δ-C_{20}	Methyl	64	*t*-BuOH	82	79
δ-C_{20}	Propyl	18	No solvent	90	76
δ-C_{20}	2-Ethylhexyl	130	*t*-BuOH	82	52

[a]R–NH–$C_6H_{13}O_5$.
[b]High-performance liquid chromatography (HPLC) yields.
[c]Isolated yield.

TABLE 2
Synthesis of 1-(*N*-propyl-5-hydroxy eicosamido)-D-Glucitol Under Various Conditions

Solvent	Reaction time (h)	Catalyst	Temperature (°C)	Yield (%)[a]
i-PrOH	26	—	82	57
t-BuOH	80	—	82	77
t-BuOH	24	Chirazyme L-1	50	22
t-BuOH	48	Trimethylamine	82	0
t-BuOH	48	Sodium methoxide	82	0
None	18	—	90 (melt)	76
None	24	—	105–135 (melt)	0

[a]HPLC yields. See Table 1 for abbreviation.

Using the synthesis of 1-(*N*-propyl-5-hydroxy eicosamido)-D-glucitol (**VII**) as a model compound, other reaction parameters were investigated (Table 2). Among several solvents, only 2-propanol and *t*-butyl alcohol dissolved both reagents. The reaction in 2-propanol gave lower yields than the same reaction in *t*-butyl alcohol. Several catalysts were tried unsuccessfully. Temperatures lower than 80°C led to longer reaction times and temperatures greater than 90°C led to color development as well as reduced yields. In solventless reactions, the minimum temperature was dictated by the melting point of the δ-lactone. Where miscibility was a problem, the temperature of solvent reflux was the limiting factor, but there were indications that small amounts of reaction products helped to increase reactants miscibility. In addition, removal of the solvent by distillation may be possible after initial product formation has occurred, thereby allowing elevated temperatures, increased rates and yields.

Some of the 1-(*N*-alkyl-5-hydroxy fatty acid amido)-D-glucitols should prove to have utility as co-surfactants in different applications. The syntheses are rapid, with little or no solvent, and in some cases the reaction product is acceptable for most uses without further purification.

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